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Investigation of the level of PAPP-A and ceruloplasmin in pericardial fluid in patients with open heart surgery

PAPP-A and ceruloplasmin level in pericardial fluid

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Abstract
Aim: PAPP-A is a specific activator of insulin-like growth factor I (IGF-I), which plays a role in the development of atherosclerosis by acting on the smooth muscle cells of the vessels. Ceruloplasmin, on the other hand, is an acute-phase protein with 7-8% carbohydrate content and a moderate response to inflammation. In our study, it was aimed to determine the level of PAPP-A, Ceruloplasmin, PON1, Arylesterase, TOS, TAS and OSI values filtered into the pericardial fluid of patients undergoing open heart surgery for cardiovascular diseases.
Material and Methods: Forty patients who were operated on by the cardiopulmonary bypass method were included in this study. Pericardial fluid was taken from these patients and PAPP-A with the ELISA method, Ceruloplasmin with the Erel method, PON1 and Arylesterase were studied with the rel assay kit. In addition, Total Antioxidant Stress (TAS), Total Oxidative Stress (TOS) and Oxidative Stress Index (OSI) measurements were also made.
Results: As a result of the study, no significant correlation was found between PAPP-A and Ceruloplasmin. There was a negative correlation (r=-0.509) between ceruloplasmin and Arylesterase, and a significant correlation was found between them ($p=0.022$, $p<0.05$).
Discussion: PAPP-A and ceruloplasmin values have been shown to be important in terms of protection against atherosclerosis during cardiopulmonary bypass. With these parameters, which have been observed to have protective effects against the formation of atherosclerosis and against atherosclerosis, possible cardiac damage can be prevented by therapeutic strategies that reduce myocardial damage.

Keywords
Cardiopulmonary Bypass, PAPP-A, Ceruloplasmin, Paraoxonase, Arylesterase

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Introduction

Cardiovascular disease (CVD) is a syndrome characterized by a structural or functional heart abnormality that results in decreased cardiac output or high intracardiac pressures at rest or during stress [1].

Cardiopulmonary bypass (CPB) has clarified one of the most difficult questions in the history of medicine, such as "Can we operate on the human heart without killing the patient?" With the dawning of a new era for cardiac surgery, a bloodless environment has been created that allows surgeons to open and repair the heart efficiently and deliver warm oxygenated blood to the rest of the heart without disrupting the heart's work [2,3].

Recently, pericardial fluid (PF) has been used in addition to blood and heart tissue in the diagnosis of CVDs. PF analysis provides insight into many pathophysiological mechanisms in a variety of pericardial and CVD. Many studies to compare cardiac biomarkers have had better results from PF studies than from blood plasma [4].

PF is a biologically active part of the heart that communicates with the myocardial interstitium and creates a unique cardiac microenvironment [5]. This fluid contains many bioactive compounds thought to be products of serum ultrafiltration and leakage from the myocardium into the pericardial space [6].

The pregnancy-associated plasma protein-A (PAPP-A) enzyme has been shown to be an important regulator of local insulin-like growth factor (IGF) signaling and exhibits proatherogenic activity [7]. PAPP-A is responsible for the cleavage of IGF-binding protein-4 (IGFBP-4) in many tissues and is effective in increasing the density of IGF. Studies have reported that PAPP-A plays an important role in the formation of atherosclerosis, and circulating PAPP-A concentrations are associated with cardiovascular risk and acute disease [8].

Ceruloplasmin (Cp), also known as copper oxidase, is a blue-looking copper glycoprotein that was first purified from human serum α2-globulin in 1948 by Holmberg and Laurell. SP exists in two molecular isoforms, secreted SP (sSP) and a membrane glycosylphosphatidylinositol (GPI) associated CP (GPI-SP). sSP is mainly produced by the liver [9].

Cp has multiple physiological functions. It plays important roles in transporting 40-70% of Cu in plasma, iron (Fe) regulation, free radical scavenging and antioxidant processes [10].

Paraoxonase, on the other hand, is a glycoprotein enzyme and a calcium-dependent ester hydrolase with both arylesterase (E.C. 3.1.1.2) and paraoxonase (E.C.3.1.8.1) activities. Paraoxonase has three different structures: PON 1, PON 2 and PON 3. This enzyme is encoded in the long arm of chromosome 7q 21.3 22.1. PON 1 is synthesized by the liver and released into the blood [11].

Considering all this information in our study, the aim of this study is to determine the level of PAPPA, Ceruloplasmin, PON1, Arylesterase, TOS, TAS and OSI values filtered into the pericardial fluid of patients who have undergone open heart surgery for various cardiovascular diseases in cardiovascular diseases, to analyze the relationship between these parameters and CVD, and thus to contribute to the understanding of the pathophysiology of the disease.

Material and Methods

Ethics committee approval

This study was approved by the Harran University Faculty of Medicine Clinical Research Ethics Committee, with the decision dated 01.04.2016, session 03 and number 64.

Patients included in the study

This study was conducted in accordance with the Helsinki Declaration, which was revised in 1989. A total of 40 patients who were operated with the cardiopulmonary bypass method were included in this study. The study group was formed by taking pericardial fluid after sternotomy from the patients included in the study.

Obtaining Pericardial Fluid

After median sternotomy was performed with standard cardiopulmonary bypass procedures in patients who underwent open heart surgery, the pericardium was opened and pericardial fluid was aspirated with a sterile syringe. Pericardial fluid was then collected in sterile tubes without anticoagulant. The sterile tube from which the pericardial fluid was taken was immediately transferred into an ice-filled container. Then, the pericardial fluid in the sterile tube was passed through the centrifugation step. Then, the supernatant part was taken into a sterile Eppendorf tube and stored at -80 for analysis.

Study of Pericardial Fluid Samples

Elabscience Human PAPP-A ELISA Kit was used for this study. PAPP-A ELISA kit works according to the Sandwich-ELISA method. Before the study, the pericardial fluid of 40 patients, which was removed from –80 °C, was brought to room temperature and expected to dissolve. It was then centrifuged at 1000 g at +4 degrees for 20 minutes. The study was started by transferring the supernatant part on the Eppendorf tube to another Eppendorf tube.

Ceruloplasmin (Ferroxidase) Level Measurement

The ferro-oxidase enzyme activity of ceruloplasmin was measured according to the Erel method. This method involves the oxidation of ferrous iron ion to ferric iron ion. Results were expressed as U/L [12].

Paraoxonase Enzyme Activity Measurement

Paraoxonase activity, a lipophilic, hydrophobic antioxidant enzyme linked to HDL-Cholesterol, was measured using a commercial Rel Assay kit. The absorbance of the formed product was monitored in the kinetic mode at 412 nm, and the enzyme activity was expressed as U/L [13].

Arylesterase Activity Measurement

Arylesterase activity of paraoxonase enzyme, an antioxidant enzyme, was measured using a commercial Rel Assay kit. Results were expressed in kU/L as the enzyme activity is at very high levels [14].

Measurement of Antioxidant and OS Parameters in PF

Total Antioxidant Status (TAS) Measurement

TAS measurement in PF was performed using the Rel Assay Diagnostics total oxidant capacity measurement kit (Rel Assay Diagnostics, Lot. No: HN20106A, Turkey). Plasma TAS levels were determined using a new automated measurement method developed by Erel [15].

Total Oxidant Status (TOS) Measurement

Rel Assay Diagnostics total oxidant capacity measurement kit (Rel Assay Diagnostics, Lot. No: OK20115O, Turkey) was

used for TOS measurement in PF. Plasma TOS levels were determined using a new automated measurement method developed by Erel [16].

Oxidative Stress Index (OSI) Measurement

OSI was calculated by dividing Total Oxidant Level (TOS)/Total Antioxidant and expressed as Arbitrary Unit (AU).

Statistical analysis

Statistical analyzes were performed using the SPSS Version 17 (SPSS Inc. Chicago USA) computer program. The significance of the difference between the means of the groups was compared with the One-Way ANOVA test. The relationship between the parameters was investigated by Pearson's correlation analysis. Values less than $p < 0.05$ were considered statistically significant.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

Demographic Data of the Working Group

Of the patients included in the study, 12 were female and 28 were male, and the mean age was 60.97 years. Demographic data of 40 patients included in the study are shown in Table 1.

ELISA Results in PF

Optical density results read at 450 nm using commercial kits for PAPP-A and Ceruloplasmin level determination in PF by ELISA method and the results of Paraoxonase, Arylesterase, OS Parameters are shown in Table 2.

At the values indicated in Table 2, the lowest value of PAPP-A in the pericardial fluid of the patients was 3.19 ng/mL, the highest value was 10.61 ng/mL, and the mean was 5.83 ng/mL. When the ceruloplasmin values were examined, the lowest value was 432 U/L, the highest value was 763 U/L, and the average was 638 U/L. The paraoxonase value was found to be a minimum of 21 U/L, a maximum of 100 U/L, and an average of 67 U/L. Arelisterase values were found to be a minimum of 321 U/L, a maximum of 399 U/L, and an average of 368 U/L. The OSI average value was 1.11, the minimum value was 0.38, and the maximum value was 1.67 arbitrary units.

When the correlation between PAPP-A and ceruloplasmin was examined, although there was a negative relationship between these two parameters (r=-0.399), there was no significant relationship between them (p=0.081, p>0.05).

When the correlation between ceruloplasmin and Arylesterase was examined, a negative relationship was found between these two parameters (r=-0.509) and a significant relationship between them was revealed (p=0.022, p<0.05).

When the correlation between paraoxonase and arylesterase was examined, although there was a positive correlation between the two (r=0.039), no significant relation was found between them (p=0.871, p>0.05).

Considering the correlation between paraoxonase and OSI value, although there was a negative relationship between the two parameters (r=-0.104), there was no significant relationship between them (p=0.663, p>0.05).

Table 1. Demographic characteristics of the patients included in the study.

Variable ±	Patients (n=40)
Gender (Male/Female) %	% 28/12 (% 70 / % 30)
Age (years)	Minimum: 38,00
	Maximum: 85,00
	Mean: 60,9706

Table 2. Minimum, Maximum, Mean and Standard Deviation Results of Pericardial PAPP-A, Ceruloplasmin, Paraoxonase, Arylesterase and Antioxidant Levels in Patients.

	Minimum	Maximum	Mean	Standard Deviation
TAS (Trolox equivalent/L)	0,9	1,68	1,334	0,17901
TOS (μmol H_2O_2 Eqv./L)	5,7	19	14,5875	2,96044
OSI (Arbitrary Unit (AU))	0,38	1,67	1,1112	0,25381
Pericardium PAPP-A (ng/mL)	3,19	10,61	5,8305	1,93161
Pericardium Ceruloplasmin (U/L)	432	763	638,3	71,19957
Paraoxonase (U/L)	21	100	67,91	19,72111
Arylesterase (U/L)	321	399	368,52	17,78363

Table 3. Correlation Analysis of Variables

		PAPP-A	Ceruloplasmin	Paraoxonase	Arylesterase	TAS	TOS	OSI
PAPP-A	r	1	-0,399	0,256	0,242	-0,324	0,1	0,359
	p		0,081	0,275	0,303	0,163	0,675	0,12
Ceruloplasmin	r	-0,399	1	0,076	-,509*	,525*	-0,309	-,644**
	p	0,081		0,751	0,022	0,017	0,185	0,002
Paraoxonase	r	0,256	0,076	1	0,039	-0,032	-0,178	-0,104
	p	0,275	0,751		0,871	0,893	0,453	0,663
Arylesterase	r	0,242	-,509*	0,039	1	-0,282	-0,242	0,009
	p	0,303	0,022	0,871		0,228	0,303	0,969
TAS	r	-0,324	,525*	-0,032	-0,282	1	0,115	-,544*
	p	0,163	0,017	0,893	0,228		0,628	0,013
TOS	r	0,1	-0,309	-0,178	-0,242	0,115	1	,755**
	p	0,675	0,185	0,453	0,303	0,628		0
OSI	r	0,359	-,644**	-0,104	0,009	-,544*	,755**	1
	p	0,12	0,002	0,663	0,969	0,013	0	

*. The correlation is significant at the 0.05 level; **. The correlation is significant at the 0.01 level; The correlation results are shown in Table 3.

Considering the correlation between Arylesterase and OSI, although there was a positive correlation (r=0.009), no significant correlation was found between these two parameters (p=0.969, p>0.05).

Considering the correlation between PAPP-A and OSI value, although there was a positive relationship between the two parameters (r=-0.359), there was no significant relationship between them (p=0.120, p>0.05).

Considering the correlation between PAPP-A and paraoxonase, although there was a positive correlation (r=0.256), no significant correlation was found between these two parameters (p=0.275, p>0.05).

When the relationship between PAPP-A and arylesterase was examined, although there was a positive relationship between these two parameters (r=-0.242), there was no significant relationship between them (p=0.303, p>0.05).

When the correlation between PAPP-A and ceruloplasmin was examined, although there was a negative relationship between these two parameters (r=-0.399), no significant relationship was found between them (p=0.081, p>0.05).

Discussion

In addition to blood and heart tissue, PF can be used to diagnose CVD. PF analysis may not provide an understanding of many pathophysiological systems in various pericardial and cardiovascular diseases [17].

In this study, we aimed to determine the level of PAPP-A, Ceruloplasmin, Paraoxonase, Arylesterase, TOS, TAS and OSI values in CVD that filtered into the pericardial fluid of patients who had open heart surgery, to analyze the relationship between these parameters and CVD, and thus to contribute to the understanding of the pathophysiology of the disease.

With the emergence of the concept of fragile plaque, studies on the diagnosis and treatment of fragile plaque have increased. However, many studies have indicated that high PAPP-A activity contributes to the formation of an atherogenic environment. In a study in mice, it was stated that transgenic overexpression of PAPP-A accelerated plaque progression, while the absence of PAPP-A caused an 80% reduction in plaque development [7]. In the studies, the function of the IGF system in cardiac dysfunction and CVD has been the subject of much debate, and there are conflicts as to whether the IGF system mainly exerts proatherogenic or atheroprotective functions. Studies have shown that high PAPP-A activity supports the theory that it supports an atherogenic environment. Transgenic overexpression of PAPP-A in mice accelerated plaque progression, while the absence of PAPP-A resulted in an 80% reduction in plaque development. [18].

In a study conducted, total concentration of IGF in the pericardial fluid was found to be 72% ± 10% lower than the plasma concentration, while the PAPP-A concentration was reported to be approximately 15 times more concentrated. They reported that 2 IGFBP-4 produced by PAPP-A and reflecting PAPP-A activity increased approximately more than 25% from the baseline levels. They found that IGF bioactivity was 62 ± 81% higher in pericardial fluid than in plasma [19]. In our study, the lowest value of PAPP-A in the pericardial fluid of the patients was 3.19 ng/mL, the highest value was 10.61 ng/mL, and the mean was 5.83 ng/mL.

In a study with 40 stable coronary patients and 20 normal coronary patients, it was observed that the ceruloplasmin value increased after approximately 48 hours by examining the rise of acute phase reactants immediately after the stent was placed in stable angina pectoris patients. In addition, it was observed that the serum ceruloplasmin level was higher in patients with Pulmonary Artery Disease than in patients without [20]. In our study, when the ceruloplasmin values in the pericardial fluid of our patients who underwent open heart surgery were examined, the lowest value was 432 U/L, the highest value was 763 U/L, and the mean was 638 U/L. When the correlation between PAPP-A and ceruloplasmin was examined, although there was a negative correlation between these two parameters (r=-0.399), no significant correlation was found between them (p=0.081, p>0.05).

In recent years, PON1 has been shown to inhibit LDL oxidation, prevent or slow down atherosclerotic formation by preventing oxidation of HDL particles and other mechanisms, and it has been investigated whether it can be a protective factor for cardiovascular diseases. At the same time, PON1 is also found in the normal arterial wall and its concentrations increase gradually in the atherosclerotic process [21].

In another study, they revealed that PON-1 arylesterase activity was significantly lower in the CAD group compared to the controls (p < 0:0001). They reported that PON-1 arylesterase activity in CAD patients was significantly higher in nondiabetic CAD patients compared to diabetic patients. (p = 0:03). PON-1 activity was found to be significantly lower in CAD patients [22]. In our study, the Arylesterase value was found to be a minimum of 321 U/L, a maximum of 399 U/L, and an average of 368 U/L. OSI average value is 1.11, minimum value is 0.38, and maximum value is 1.67 arbitrary units.

Conclusion

In conclusion, in this study, no significant correlation was found between PAPP-A and Ceruloplasmin. There was a negative correlation (r=-0.509) between ceruloplasmin and Arelisterase, and a significant correlation was found between them (p=0.022, p<0.05). In the literature review, no study was found showing the distribution of these parameters in the pericardial fluids of patients who were taken to cardiopulmonary bypass for various reasons, and the presence of a relationship between them. When these results in our study are compared, we think that studies with larger and specific patient groups are needed to explain the relationship between the parameters and cardiovascular diseases, since the studies do not support each other. We think that statistically significant results can be found when patient groups are formed, the number is increased and new studies with the same and similar parameters are performed.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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